Clinical trial results:
Immunogenicity of the Inactivated, Split-Virion Influenza Vaccine Administered by the Intradermal Route in Comparison with Intramuscular Vaccination with Vaxigrip® in Adults.

Summary

EudraCT number	2005-002401-23
Trial protocol	DE BE
Global end of trial date	02 July 2008

Results information

Result version number	v1 (current)
This version publication date	05 February 2016
First version publication date	27 September 2014

Trial information

Trial identification

Sponsor protocol code	GID15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00258934
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi Pasteur SA
Sponsor organisation address	1541, Avenue Marcel Mérieux, Marcy L'Etoile, France, 69280
Public contact	Director, Clinical Development, Sanofi Pasteur, SA, 33 4 37 37 58 50 , Stephanie.pepin@sanofipasteur.com
Scientific contact	Director, Clinical Development, Sanofi Pasteur, SA, 33 4 37 37 58 50 , Stephanie.pepin@sanofipasteur.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the vaccine administered by the intradermal (ID) route with the new Becton Dickinson (BD) ID system (pre-filled ID system allowing a better ergonomic use) is at least as immunogenic as the administration of the vaccine by the intramuscular (IM) route after the first vaccination.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment were also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable.

Evidence for comparator:

Same vaccine with a different route of administration. An earlier study in 2002, GID01 conducted in 300 Lithuanian adult subjects assessed three dosages (3 µg, 6 µg, and 9 µg of each HA per strain) administered with an intradermal (ID) system, one dosage (3 µg of each HA per strain) administered with a classic ID syringe, and, as a reference, Vaxigrip® IM (containing 15 µg of each HA per strain), showed that the trivalent inactivated split-virion influenza vaccine induced a similar immune response as measured by geometric mean of titers (GMTs), when administered by the IM route or the ID route.

Actual start date of recruitment	19 September 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 750
Country: Number of subjects enrolled	Germany: 150
Country: Number of subjects enrolled	Switzerland: 78
Worldwide total number of subjects	978
EEA total number of subjects	900

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	978
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled and vaccinated from 19 September 2005 to 21 November 2005, at 4 clinical centers in Belgium, Germany and Switzerland. They got a second vaccination (Year 1) from 20 September 2006 to 31 October 2006, and a third vaccination (Year 2) from 24 September 2007 to 07 November 2007.

Pre-assignment

Screening details:

A total of 978 subjects who met all the inclusion, but none of the exclusion criteria were enrolled and vaccinated in the study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Intradermal Vaccination Group

Arm description:

Subjects received 9 µg dose influenza vaccine by the intradermal route on Day 0 (first vaccination)

Arm type	Experimental
Investigational medicinal product name	Intradermal Influenza Vaccine
Investigational medicinal product code	333
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intradermal use

Dosage and administration details:

0.1 mL (9 µg) single annual dose, intradermal into the upper arm (deltoid area)

Arm title	Intramuscular Vaccine Group

Arm description:

Subjects received 15 µg dose influenza vaccine by the intramuscular route on Day 0 (first vaccination)

Arm type	Active comparator
Investigational medicinal product name	Intradermal Influenza Vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL (15 µg) single annual dose, intramuscular into the upper arm (deltoid area)

Number of subjects in period 1	Intradermal Vaccination Group	Intramuscular Vaccine Group
Started	588	390
Completed	588	390

Baseline characteristics

Reporting groups	
Reporting group title	Intradermal Vaccination Group
Reporting group description:	
Subjects received 9 µg dose influenza vaccine by the intradermal route on Day 0 (first vaccination)	
Reporting group title	Intramuscular Vaccine Group
Reporting group description:	
Subjects received 15 µg dose influenza vaccine by the intramuscular route on Day 0 (first vaccination)	

Reporting group values	Intradermal Vaccination Group	Intramuscular Vaccine Group	Total
Number of subjects	588	390	978
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	588	390	978
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	40.1	40.2	
standard deviation	± 10.9	± 11.2	-
Gender categorical Units: Subjects			
Female	367	245	612
Male	221	145	366
Previous influenza vaccination Units: Subjects			
Yes	229	147	376
No	344	231	575
Unknown	15	12	27

End points

End points reporting groups

Reporting group title	Intradermal Vaccination Group
Reporting group description:	
Subjects received 9 µg dose influenza vaccine by the intradermal route on Day 0 (first vaccination)	
Reporting group title	Intramuscular Vaccine Group
Reporting group description:	
Subjects received 15 µg dose influenza vaccine by the intramuscular route on Day 0 (first vaccination)	

Primary: Geometric Mean Titers of Antibodies to Influenza Antigens Before and After either Intradermal or Intramuscular Influenza vaccination

End point title	Geometric Mean Titers of Antibodies to Influenza Antigens Before and After either Intradermal or Intramuscular Influenza vaccination
End point description:	
End point type	Primary
End point timeframe:	
Day 0 (pre-vaccination) and 21 days Post-vaccination	

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	381	379		
Units: Titers				
geometric mean (confidence interval 95%)				
A/ H1N1 (Pre-vaccination)	15.3 (13.3 to 17.7)	14.6 (12.7 to 16.7)		
A/ H3N2 (Pre-vaccination)	29.4 (25.6 to 33.7)	27.1 (23.9 to 30.7)		
B (Pre-vaccination)	12 (10.8 to 13.3)	11.3 (10.3 to 12.5)		
A/ H1N1 (Post-vaccination)	249 (216 to 287)	199 (170 to 232)		
A/ H3N2 (Post-vaccination)	828 (738 to 928)	571 (502 to 649)		
B (Post-vaccination)	144 (129 to 161)	124 (110 to 139)		

Statistical analyses

Statistical analysis title	Non-inferiority test of ID Group for A/H1N1 Strain
Statistical analysis description:	
For each strain, the primary parameter was the difference of the log10 transformation of post-	

vaccination geometric mean of titer between the compared vaccine groups. For each strain, the hypotheses tested were as follows:
H0: log10(GMTID)-log10(GMTIM) ≤ -0.176 which is equivalent to GMTIM / GMTID ≥ 1.5
H1: log10(GMTID)-log10(GMTIM) > -0.176 which is equivalent to GMTIM / GMTID < 1.5
The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain

Comparison groups	Intradermal Vaccination Group v Intramuscular Vaccine Group
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	2-Sided Confidence Interval
Parameter estimate	Median difference (final values)
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.189

Notes:

[1] - The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain.

Statistical analysis title	Non-inferiority test of ID Group for A/H3N2 Strain

Statistical analysis description:

For each strain, the primary parameter was the difference of the log10 transformation of post-vaccination geometric mean of titer between the compared vaccine groups. For each strain, the hypotheses tested were as follows:
H0: log10(GMTID)-log10(GMTIM) ≤ -0.176 which is equivalent to GMTIM / GMTID ≥ 1.5
H1: log10(GMTID)-log10(GMTIM) > -0.176 which is equivalent to GMTIM / GMTID < 1.5
The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain

Comparison groups	Intradermal Vaccination Group v Intramuscular Vaccine Group
Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	2-Sided Confidence Interval
Parameter estimate	Median difference (final values)
Point estimate	0.162
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.236

Notes:

[2] - The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain.

Statistical analysis title	Non-inferiority test of ID Group for B Strain

Statistical analysis description:

For each strain, the primary parameter was the difference of the log10 transformation of post-vaccination geometric mean of titer between the compared vaccine groups. For each strain, the hypotheses tested were as follows:
H0: log10(GMTID)-log10(GMTIM) ≤ -0.176 which is equivalent to GMTIM / GMTID ≥ 1.5
H1: log10(GMTID)-log10(GMTIM) > -0.176 which is equivalent to GMTIM / GMTID < 1.5
The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain

Comparison groups	Intradermal Vaccination Group v Intramuscular Vaccine Group

Number of subjects included in analysis	760
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	2-Sided Confidence Interval
Parameter estimate	Median difference (final values)
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.136

Notes:

[3] - The ID group was considered as non-inferior to the IM group if the hypothesis H0 was rejected for each strain.

Secondary: Percentage of Subjects with Seroprotection Against Influenza Antigens Before and After First Vaccination with either Intradermal or Intramucular Influenza Vaccine

End point title	Percentage of Subjects with Seroprotection Against Influenza Antigens Before and After First Vaccination with either Intradermal or Intramucular Influenza Vaccine

End point description:

Influenza virus antibodies were measured by the hemagglutination inhibition (HI) technique. Seroprotection was defined as an antibody titer of ≥40 1/dilution.

End point type	Secondary

End point timeframe:

Day 0 (pre-vaccination) snd 21 Days Post-vaccination (First vaccination)

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	385		
Units: Percentage of Subjects				
number (not applicable)				
A/H1N1 (Pre-vaccination)	27.7	26.2		
A/H3N2 (Pre-vaccination)	43.9	40.9		
B (Pre-vaccination)	16.8	16.6		
A/H1N1 (Post-vaccination)	92.4	88.8		
A/H3N2 (Post-vaccination)	99.7	98.7		
B (Post-vaccination)	90.6	85.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Seroconversion or Significant Increase in Influenza Antibodies Post-vaccination with either an Intradermal or Intramucular Influenza Vaccine

End point title	Percentage of Subjects with Seroconversion or Significant Increase in Influenza Antibodies Post-vaccination with either an Intradermal or Intramucular Influenza Vaccine

End point description:

Influenza antibodies were measured using the hemagglutination inhibition (HI) technique. Seroconversion was defined as a pre-vaccination titer <10 (1/dil): post-injection titer ≥40 (1/dil) on Day 21; Significant increase was defined as a pre-vaccination titer ≥10 (1/dil): ≥4-fold increase from pre- to post-injection titer on Day 21.

End point type	Secondary

End point timeframe:

21 Days post-vaccination

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	385		
Units: Percentage of Subjects				
number (not applicable)				
A/H1N1 (A/New Caledonia/20/99)	74.3	70.4		
A/H3N2 (A/Wellington/1/2004)	85.1	79.2		
B (B/Jiangsu/361/2002)	76.4	73.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing at Least one Reaction Listed in the EMEA Note for Guidance Within 3 days After First Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point title	Number of Subjects Experiencing at Least one Reaction Listed in the EMEA Note for Guidance Within 3 days After First Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point description:

End point type	Secondary

End point timeframe:

Within 3 Days post-vaccination (First vaccination)

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	588	390		
Units: Subjects				
Injection site induration >5 cm for > 3 days	1	0		

Injection site ecchymosis (bruising)	9	9		
Fever (rectal equivalent temperature > 30.0 C) for	9	3		
Malaise	68	56		
Shivering (Rigors)	35	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Reactions Within 7 Days After First Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point title	Number of Subjects Reporting Solicited Reactions Within 7 Days After First Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point description:

End point type	Secondary

End point timeframe:

Day 0 to Day 7 Post First Vaccination

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	588	390		
Units: Subjects				
Injection site Ecchymosis	18	10		
Injection site Erythema	505	44		
Injection site Induration	367	49		
Injection site Pain	220	149		
Injection site Pruritus	210	17		
Injection site Swelling	377	31		
Fever	20	14		
Headache	192	116		
Malaise	84	66		
Myalgia	114	113		
Shivering	38	33		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing at Least one Reaction Listed in the EMEA Note for Guidance Within 3 days After Second Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point title	Number of Subjects Experiencing at Least one Reaction Listed in the EMEA Note for Guidance Within 3 days After Second Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point description:

End point type	Secondary

End point timeframe:

Within 3 Days post-second injection

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	349		
Units: Subjects				
Injection site Induration >5 cm for >3 days	2	0		
Injetion site ecchymosis (Bruising)	15	7		
Pyrexia (rectal equivalent temp >38.0 C) for 24 hr	6	4		
Malaise	55	36		
Shivering (Rigors)	28	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Solicited Reactions Within 7 Days After Second Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point title	Number of Subjects Reporting Solicited Reactions Within 7 Days After Second Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point description:

End point type	Secondary

End point timeframe:

Day 0 up to Day 7 post-second vaccination

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	529	349		
Units: Subjects				
Injection site Ecchymosis	19	7		
Injection site Erythema	461	70		

Injection site Induration	407	78		
Injection site Pain	214	149		
Injection site Pruritus	228	37		
Injection site Swelling	330	45		
Fever	15	12		
Headache	156	88		
Malaise	70	49		
Myalgia	97	100		
Shivering	32	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Experiencing at Least One Reaction Listed in the EMEA Note for Guidance Within 3 days After Third Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point title	Number of Subjects Experiencing at Least One Reaction Listed in the EMEA Note for Guidance Within 3 days After Third Vaccination with Either an Intradermal or Intramuscular Influenza Vaccine

End point description:

End point type	Secondary

End point timeframe:

Within 3 Days After Third Vaccination

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494	324		
Units: Subjects				
Injection site Induration >5 cm for >3 days	2	1		
Injection site Ecchymosis (Bruising)	11	11		
Pyrexia (rectal equivalent temp >38.0 C) for ≥24h	8	3		
Malaise	54	33		
Shivering (Rigors)	19	25		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Antibody Persistence to Influenza Antigens Before and 21 Days,

3, 6 and 12 Months Post-vaccination with Either Intradermal or an Intramuscular Influenza Vaccine

End point title	Antibody Persistence to Influenza Antigens Before and 21 Days, 3, 6 and 12 Months Post-vaccination with Either Intradermal or an Intramuscular Influenza Vaccine

End point description:

Influenza antibodies were measured using the hemagglutination inhibition (HI) technique. Antibody persistence was defined as seroprotection, antibody titer ≥40 (1/dilution) at each defined timepoints.

End point type	Other pre-specified

End point timeframe:

Day 0 (pre-vaccination) and 21 Days, 3, 6 and 12 months post-vaccination

End point values	Intradermal Vaccination Group	Intramuscular Vaccine Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	385		
Units: Percentage of Subjects				
number (not applicable)				
A/H1N1 (Pre-vaccination)	27.7	26.2		
A/H3N2 (Pre-vaccination)	43.9	40.8		
B (Pre-vaccination)	16.7	16.6		
A/H1N1 (Day 21 Post-vaccination)	92.4	88.8		
A/H3N2 (Day 21 Post-vaccination)	99.7	98.7		
B (Day 21 Post-vaccination)	90.6	85.5		
A/H1N1 (3 Months Post-vaccination)	86.7	81.3		
A/H3N2 (3 Months Post-vaccination)	98.9	97.1		
B (3 Months Post-vaccination)	77.5	72.6		
A/H1N1 (6 Months Post-vaccination)	82	75.9		
A/H3N2 (6 Months Post-vaccination)	97.8	95.8		
B (6 Months Post-vaccination)	61.4	65.7		
A/H1N1 (12 Months Post-vaccination)	68.2	67.7		
A/H3N2 (12 Months Post-vaccination)	96.2	89.1		
B (12 Months Post-vaccination)	49.9	53.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events data were collected from Day 0 after Dose 1 through up to 6 months after the last dose	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	7.0
Reporting groups	
Reporting group title	Intradermal Vaccination Group
Reporting group description:	
Subjects received 9 µg influenza vaccine by the intradermal route on Day 0 (first vaccination)	
Reporting group title	Intramuscular Vaccine Group
Reporting group description:	
Subjects received 0.5 mL (15 µg) dose by the intramuscular route	

Serious adverse events	Intradermal Vaccination Group	Intramuscular Vaccine Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 588 (0.00%)	0 / 390 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Intradermal Vaccination Group	Intramuscular Vaccine Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 588 (5.95%)	17 / 390 (4.36%)	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	35 / 588 (5.95%)	17 / 390 (4.36%)	
occurrences (all)	35	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2005	The use of paper CRF instead of electronic CRF; Ealuation of immunogenicity in a subset of subjects following the second and third vaccinations; Definition of Serum storage and shipping temperature.
16 March 2006	The replacement of a Principal Investigator in Germany, was submitted to the German IEC only.
23 May 2006	Information on the vaccine formulation to be administered for the second vaccination (2006-2007 Northern Hemisphere) and planned the assessment of the comfort vaccination using a Verbal Rating Scale (VRS) and a Patient-Reported Outcome questionnaire: the Vaccination Comfort Questionnaire (VCQ).
19 June 2006	Before the second vaccination a modification of the immunogenicity analysis.
13 September 2006	A replacement of a Principal Investigator in Belgium was submitted to the Belgium IEC only.
10 November 2006	A replacement of a Principal Investigator in Belgium was submitted to the Belgium IEC only.
24 May 2007	Information on the vaccine formulation to be administered for the third vaccination (2007-2008 Northern Hemisphere) was provided along with notice of the change of Center Name from "MDS Pharma Germany GmbH" to "Momentum Pharma Service GmbH" and the an update to the process of documenting local reactions at the injection site; the sample preparation process, and the VCQ form and the SAEs reporting process.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable.

Notes: